Back to the Beginning: Identifying lesions of Diffuse Idiopathic Skeletal Hyperostosis prior to Vertebral Ankylosis

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ABSTRACT

Objective: To better understand the pathogenesis of DISH, identifying early or pre-DISH lesions in the spine and investigating the relationship between spinal and extra-spinal manifestations of DISH. **Material:** 44 skeletonized individuals with DISH from the WM Bass Donated Skeletal Collection. **Methods:** For each vertebra, location, extension, point of origin and appearance of vertebral outgrowths were recorded. The size of the enthesophytes at the olecranon process, patella and calcaneal tuberosity was measured with digital callipers. **Results:** At either end of the DISH-ankylosed segment, isolated vertical outgrowths arising from the central third of the anterior aspect of the vertebral body can usually be observed. These bone outgrowths show a well-organized external cortical layer, an internal structure of trabecular bone and usually are unaccompanied by or show minimal associated endplate degeneration. Analysis of the relationship between spinal and extra-spinal manifestations (ESM) suggests great inter-individual variability. No correlation between any ESM and the stage of spinal DISH was found. **Conclusions:** Small isolated outgrowths represent the earliest stages of the spinal manifestations of DISH. The use of ESM as an indicator of DISH should be undertaken with great caution until the relationship between these two features is understood. **Significance:** Improved accuracy of paleopathological diagnostic criteria of DISH**. Limitations:** Small sample comprised of only individuals with DISH. **Future Research:** micro-CT analysis to investigate the internal structure of the spinal lesions. Analysis of extra-spinal enthesophytes in individuals with and without DISH to understand their pathogenesis and association with the spinal lesions in individuals with DISH.

Key words: DISH; spinal manifestations; extra-spinal manifestations; vertebral bone outgrowths; vertebral endplate degeneration; vertebral ankylosis, enthesophytes

INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic hyperostotic condition characterized by the ossification of ligaments and tendons or adjacent structures (Mader et al. 2013). The most common manifestations are a 'flowing' ossification along the right antero-lateral aspect of the spinal column and extraspinal enthesopathies (Resnick et al. 1975; Utsinger 1985; Crubézy 1989).

The first references to DISH can be attributed to Knaggs (1925), Meyer and Forster (1938), Oppenheimer (1942) and Smith et al. (1955), who described a condition characterized by extensive ossification of the vertebral ligaments which was most extensive at the anterior longitudinal ligament of the thoracic region, less complete at the lumbar vertebrae and almost always absent in the cervical segment. Knaggs (1925) named it 'spondylitis deformans', Oppenheimer (1942), 'spondylitis ossificans ligamentosa' and Smith et al. (1955), 'physiologic vertebral ligamentous calcification'. Smith et al. (1955) also noted that the ossification of the anterior longitudinal ligament could measure up to a thickness of 5 to 10 mm with greater thickness commonly found at the level of the intervertebral disk. The authors also noted that the ossification was distinct from the anterior margins of the adjacent vertebrae and observed that sacroiliac, apophyseal and costovertebral joints appeared normal in the majority of the patients. Thus it was argued that all these changes were age-related degenerative changes, since all their patients with the disease were over 60 years of age (Smith et al. 1955).

The first diagnostic criterion of DISH described the radiographic appearance as hyperostotic bone outgrowths located mainly at the vertebral column, located at the anterolateral aspect of the vertebral bodies, and growing vertically in a “candle-flame” formation over the lumbar disk spaces (Forestier and Rotés-Querol 1950). The authors indicated that, at the level of the intervertebral disks, the outgrowths are often thickened and that the outgrowths have a dense cortex similar to that of the head of the femur, a cancellous bone infill in continuity with that of the vertebral bodies. They concluded that these outgrowths may co-exist with osteophytes, but have entirely different anatomical features” (Forestier and Rotes-Querol 1950: 329). They named it ‘senile ankylosis hyperostosis of the spine’ though it would be commonly known as Forestier’s disease (Rogers and Waldron 1995). Forestier and Rotés-Querol (1950) indicated that while the etiology was unknown, old age was a common feature in all the patients and half of them had also suffered severe trauma, which they suggested could precipitate the clinical signs. Most importantly, they pointed out that the spinal ossification did *not* come from the anterior vertebral common ligament (also known as anterior longitudinal ligament) and proposed that the spinal ossification arose from the continuous peri-vertebral fibrous sheath. The involvement of ligaments and connective paravertebral tissue in the formation of the spinal lesion led Forestier and Lagier (1971) to describe them as *entheseal*, a nomenclature also used by François et al. (1995), Freemont (2002) and Hannallah et al. (2007). However, currently, the majority of the osteoarchaeological research community still refer to them as DISH-osteophytes as they were described by Resnick and Niwayama (1976).

DISH is frequently identified in archaeological human remains as well as in medical practice, often associated with men over 50 years of age (Forestier and Rotes-Querol 1950; Julkunen et al. 1971; Cassim et al. 1990; Hannallah et al. 2007). However, given the "insidious evolution of the disease" and the lack of clear symptomatology for its early stages, the age of onset is difficult to identify (Forestier and Rotes-Querol 1950). DISH has been consistently related to high calorific diets, and clinical studies have linked DISH with several metabolic-related conditions including type 2 diabetes and obesity (e.g. Sarzi-Puttini and Atzeni 2004; Denko and Malemud 2006; Mader and Lavi 2009). However, its etiology still remains poorly understood.

Spinal manifestations of DISH

DISH most commonly affects the thoracic spine but, as a cranio-caudally progressive condition, it can advance to involve the cervical and the lumbar sections. The ossification on the right side of the spine is often associated with the effect of the aorta (located on the left) in preventing the bone formation as a result of its continuous pulsation (Forestier and Rotes-Querol 1950; Kuperus et al. 2018). The location of spinal ossification of the left side of the spine in cases of *situs viscerum inversus* confirms this association (Ciocci 1987; Carile et al. 1989). The fact that in the lumbar region, where the aorta descends anteriorly (Standring and Tunstall 2015: 1087), the ossification was bilateral and the bone proliferation not inhibited (Tsukamoto et al. 1977: 916) provides further evidence of the association between this location and the aorta and the distribution of DISH. Characteristically, the intervertebral disk space is maintained and the apophyseal facets are not involved in the ankylosis (Resnick and Niwayama 1976; Utsinger et al. 1976; Kacki and Villotte 2006). These features combined with the vertical orientation and the rooting of the DISH outgrowths on the side of the vertebral body help differentiate DISH from ankylosing spondylitis and spinal osteophytosis (Forestier and Rotes-Querol 1950;

Crubézy 1989; Chanchairujira et al. 2004). This vertical configuration of the DISH-outgrowths also distinguishes them from the osteophytes associated with discarthrosis (Table 1). In paleopathology, discarthrosis is characterized by the presence of horizontal spinal osteophytes rooted at the edge of the vertebral endplate and by endplate degeneration associated with the loss of water content and structural changes of the intervertebral disk (Prescher 1998; Steinbock 1976; François et al. 1995; Maat et al. 1995). Spinal osteophytes are usually accompanied by changes to the endplate (Maat et al. 1995), which can be observed even if osteophytes are obscured by DISH outgrowths. Spinal osteophytes have been associated with higher BMI and increasing age (Forestier and Rotes-Querol 1950; Utsinger 1985; Denko and Malemud 2006; Watanabe and Terazawa 2006; Listi and Manheim 2012).

Beyond its etiology, the pathogenesis and diagnostic criteria of DISH are still confusing and lack consensus (Kuperus et al. 2017). There have been a significant number of attempts to define accurate diagnostic criteria, resulting in four criteria described for medical purposes (Forestier and Rotes-Querol 1950; Resnick and Niwayama 1976; Arlet and Mazières 1985; Utsinger 1985) and five more for archaeological human remains (Crubézy 1989; Crubézy and Crubézy-Ibanez 1993; Rogers and Waldron 1995; Kacki and Villotte 2006) (see table 2 for a summary of the diagnostic criteria). Van der Merwe and colleagues (2012) demonstrated, however, that when five of these methods (Resnick and Niwayama 1976, Arlet and Mazières 1985, Utsinger 1985 and Rogers and Waldron 1995) were applied to the same skeletal sample, the calculated prevalence of DISH was significantly different depending on the method applied. The authors suggested these results were due to several factors: the number of ankylosed vertebrae required to provide a positive diagnosis, the inclusion (or not) of extra-spinal manifestations in the criteria, and the acceptance of the co-occurrence of DISH and degenerative disk disease and the involvement of the sacro-iliac joint (van der Merwe et al. 2012). Similar inconsistencies were shown by Diederichs et al. (2011) who applied Resnick and Niwayama's (1975) and Mata's et al. (1998) methods to a North American sample of living elderly men of over 65 years of age. Resnick and Niwayama (1976) defined DISH as the presence of four or more vertebral bodies with continuous ossification of the anterior spinal ligaments and absence of degenerative disk disease, while Mata el at. (1998) developed a radiographic scoring system consisting of four categories: a) no ossification present, b) ossification present without bridging, c) ossification present with incomplete bridging of the disk space and, d) complete bridging of the disk space by ossification. Diederichs and colleagues' (2011) results show that, if the first method was applied, 38 patients in their sample of 342 were positively diagnosed with DISH, whereas 52 were positively diagnosed when the second method was applied.

DISH is a progressive disease with an arbitrary number of vertebrae involved in the ankylosis (three to four ankylosed vertebrae) required to issue a positive diagnosis (see table 2). To reach such an advanced stage, the condition might have been in active development for over a decade (Mader 2008; Yaniv et al. 2014). This means that none of the diagnostic criteria consider the early stages of pathogenesis. Some authors have reported probable or possible DISH in cases when advanced outgrowths that have not completely fused (i.e. interlocking outgrowths) have been observed, but the number of vertebrae involved in the ankylosis did not reach the minimum imposed threshold for diagnosis (Crubézy 1989; Kacki and Villotte 2006; Paja et al. 2010). So, while these attempts recognize the progressive nature of DISH, they did not intend to investigate how the disease process starts nor to identify the characteristic vertebral outgrowths of DISH at the initial stages of pathogenesis.

More recently, significant contributions have been made to understanding the natural progression of DISH. First, Yaniv et al. (2014) carried out CT examination of 26 patients who fulfilled Resnick's criteria for DISH and who had had at least two CT examinations of the same spinal part with a minimum of three years apart. The authors developed a semi-quantitative scoring system with 6 grades to evaluate the "osteophyte" progression, from no changes to bridging between calcified anterior longitudinal ligament/superior and inferior "osteophytes". As each grade took an average of 1.6 years to be completed, the authors concluded that a bridge was completed in around 10 years and suggested that the verticality of the majority of the "osteophytes" suggested an inflammatory rather than a degenerative pathogenesis (Yaniv et al. 2014: 1956). Kuperus et al. (2019) selected 1367 male patients of more than 50 years old (with no pre-diagnosis of DISH required) with at least two CT scans performed at least 2.5 years apart to develop new criteria. This was validated on a group of 2267 participants. The new scoring system assigns grades to each vertebral segment from 0 – no bone formation to 3 – complete bridging between the vertebral bodies above and below the disk with abundant new bone formation in more than two sagittal or coronal CT sections (with a section thickness of 1 mm) (Kuperus et al. 2019: 423). This final stage corresponds with Resnick and Niwayama's *definite* DISH. The authors reported a high sensitivity (96%) and high specificity (83%) of the new criteria with an almost perfect inter-observer and intra-observer agreement (0.75-0.89 and 0.89, respectively) (Kuperus et al. 2019: 424) and concluded that this criteria could be used in the clinical as well as the research environment.

Extra-spinal manifestations of DISH (ESM)

Sutro et al. (1956) and Harris et al. (1974) noted that the spinal manifestations were accompanied with extra-spinal enthesopathies, but the first systematic analysis of the type and location of the extra-spinal abnormalities was authored by Resnick and colleagues in

1975. Because of its diffuse distribution and the hyperostotic character, the authors named the condition *diffuse idiopathic skeletal hyperostosis* (DISH), the name now preferred by the scientific and clinical communities (François et al. 1995; Resnick 2002: 1477).

In their original 1975 paper, Resnick and colleagues reported the results of a radiographic study from 21 individuals with DISH and described the extra-spinal manifestations (ossification of extra-spinal ligaments and tendons). The areas most prone to show entheseal changes were: the tendons of *M. triceps brachii* (at the ulnar olecranon process), *Mm. quadriceps femoris* (proximal surface of patella and tibial tuberosity), *M. gastrocnemius* and *M. soleus* (calcaneal tuberosity) and of the internal and external oblique muscles (iliac crest) as well as the sacro-iliac and the ilio-lumbar ligaments. The uni- or bi-lateral ossification of the sacro-iliac ligaments associated with DISH is characteristically peri-articular, contrasting with the intra-articular fusion of the sacro-iliac joint in seronegative arthropathies (Rogers and Waldron 1995: 50).

Resnick et al. (1975) and Utsinger (1985) considered the presence of ossified ligaments as a strong enough feature to suggest a positive diagnosis of DISH, even in the absence of spinal radiographs. However, the inclusion of extra-spinal manifestations in the diagnostic criteria is not universal; in fact, only Utsinger's (1985) diagnostic criteria specifically includes them and Resnick and Niwayama (1976) only considered spinal features to evaluate the prevalence of DISH their study of in 215 individuals. In 2013, a survey study aimed at understanding levels of consensus among experts showed that within the medical community there was little agreement among clinicians and orthopaedic surgeons about the presence of the extra-spinal manifestations previously reported in patients with DISH. Therefore, in the clinical sphere, the relationship between the spinal and the extra-spinal manifestations is still being discussed, and attempts at creating new diagnostic criteria have shown that experts still disagree in the relationship between these two manifestations (Mader et al. 2012, Kuperus et al. 2017).

From an osteoarchaeological point of view, the association of the spinal and the extra-spinal manifestations has not been investigated, and DISH is usually considered a pathological condition characterized by spinal ossification *and* extra-spinal markers. In fact, ESM are more formally included in criteria derived from and applied to archaeological material (see table 2). This is possibly due to the fragmentary nature of the archaeological human remains and because the identification of ESMs in skeletonized remains is significantly easier than in living patients. In paleopathology, when the vertebrae have not been sufficiently preserved, the presence of widespread enthesopathies has, in some cases, been considered to be enough to issue a positive diagnosis of DISH (Crubézy 1989; Crubézy and Crubézy-Ibanez 1993). However, this approach could potentially over-estimate the prevalence of DISH since the presence of enthesopathies is also an age-related condition (Alves Cardoso and Henderson 2010; Milella et al. 2012). Rogers and colleagues (1997) suggested that individuals prone to extensive enthesophyte formation (including individuals with DISH) also tend to develop osteophytes, these individuals were named ‘bone formers’. Patients with DISH have been previously described as suffering from an ossifying diathesis and as having the propensity to develop ossifications in response to surgery (Resnick et al. 1978: 185; Fahrer et al. 1988). Finally, the positive association between metacarpal cortical thickness and ossification of the anterior longitudinal ligament – when age, sex and other confounding factors were controlled for – was interpreted as evidence to suggest that the tendency for spinal ossification was primarily associated with a reduced resorption at the endosteal layer of the bone (Mays 2016). These findings reinforce the characterization of DISH as an ossifying diathesis.

The aims of the study presented here are two-fold: first, to increase understanding of the pathogenesis of DISH before ankylosis; and second, to investigate the association between spinal fusion and the development of extra-spinal manifestations.

MATERIAL AND METHODS

The remains of 44 individuals (31 males and 13 females) between the ages of 51 and 89 (most common age range: 59.6 - 69.5) from the WM Bass Donated Skeletal Collection (University of Tennessee, Knoxville, USA) with DISH were analyzed to investigate the expression of the lesion. The youngest male was 51 and the youngest female 55.

All individuals had been diagnosed with DISH post-mortem, following skeletonization, using Ortner's (2003: 558-560) diagnostic criteria (Table 2). Any individual with a record of spinal surgery or trauma was excluded from the analysis to ensure traumatic ossification was not included.

The spinal segment most commonly affected by DISH is the lower half of the thoracic spine (Harris et al. 1974; Tsukamoto et al. 1977; Resnick et al. 1978). As DISH is has a slow progression rate, this suggests that the lesions start in this lower thoracic spine and progresses cranio-caudally (Kuperus et al. 2018). It is therefore hypothesized that vertically oriented entheseal changes originating on the sides of the vertebral body and located at either end of the ankylosed block of vertebrae will represent the earlier stages of development of the lesions.

In terms of nomenclature, the term "osteophyte" was not considered to be appropriate to describe the DISH-related bone outgrowths since, by definition, osteophytes are located at the margins of joints; in vertebral bodies these are horizontal outgrowths arising at the edge of the vertebral endplate (Steinbock 1976; François et al. 1995; Maat et al. 1995). The ossifying elements in the spinal manifestations of DISH are ligaments and connective paravertebral tissues, including some fibers of the anterior longitudinal ligament and the continuous perivertebral fibrous sheath. The latter is formed by short fibers inserting into two adjacent vertebrae and extending to the anterior aspect and peripheral parts of the intervertebral disk (Forestier and Rotes-Querol 1950: 329, Forestier and Lagier 1971: 69). Therefore, it would be much more accurate to describe the spinal DISH lesions as *entheseal* lesions (Forestier and Lagier 1971; François et al. 1995; Freemont 2002). Unfortunately, term has not been widely used in paleopathology; to avoid misunderstandings, the term of 'outgrowth' or 'DISH-related outgrowth' are used throughout this paper.

For each vertebra, the location, extension, point of origin and appearance of vertebral outgrowths and ankylosis was recorded. Each DISH-related outgrowth identified was classified as being isolated, interlocking but touching, or ankylosed. Table 2 shows the features used to differentiate the DISH-related outgrowths from those classified as vertebral osteophytes associated with discarthrosis or syndesmophytes.

The state of the vertebral endplate was evaluated to investigate the relationship between discarthrosis and DISH. Maat et al. (1995: 296) postulated that the increase in the prevalence of DISH in older individuals protected them from vertebral osteophytosis and vertebral osteoarthritis of the apophyseal joints. Thus the presence of discarthrosis (the presence of vertebral endplate porosity *and* horizontal osteophytes) was recorded. In cases where DISH outgrowths masked the formation of horizontal vertebral osteophytes, the presence of endplate degeneration was used to diagnose discarthrosis, as this condition always starts with the degeneration of the intervertebral disk (François et al. 1995; Prescher 1998). To evaluate this hypothesis, each vertebral endplate was evaluated, considering whether the area of the *annulus fibrosus* was unaffected by degeneration of the endplate, showed microporosity (pores of less than 1mm in diameter), microporosity associated with cortical erosion of the endplate or macroporosity (pores of more than 1mm in diameter), which we term degeneration of the endplate. Where horizontal spinal osteophytes and endplate degeneration were present, this was termed discarthrosis (François et al. 1995).

The enthesophytes more commonly associated with DISH are located at the olecranon process, the patella and calcaneal tuberosity, but neither the presence of enthesophytes, nor their distribution are solely associated with DISH. To control other enthesophyte-inducing factors Crubézy (1989) and Kacki and Villote (2006) suggested that DISH-related enthesophytes are usually symmetrical, and they measure at least 2mm in height. Thus to evaluate the relationship between spinal and extra-spinal manifestations, the size of the enthesophytes at the above-mentioned sites were measured with digital callipers from the base to the peak of the outgrowth. If the enthesis appeared without any irregularity, it was classified as *smooth;* if it showed irregularities of less than 1 mm, not effectively measurable with callipers, as *uneven;* and if it showed crested irregularities of around 1mm, as *spicules*.

Two-tailed Spearman's rho correlation analysis was used to evaluate the relationship between age-at-death of the individual, taken as the known age-at-death, and the total number of vertebrae involved in the ankylosis. Two-tailed Spearman's rho was also used to study the correlation between the number of vertebrae involved in the ankylosis and the size of the enthesophytes. The size of the enthesophytes was rounded to the nearest millimetre. In the case of multiple enthesophytes of very different sizes, the size of the largest outgrowths was used in the statistical analysis. To reduce the probability of false positives resulting from the high number of statistical operations produced, the significance threshold (p-value) was set at 0.01.

RESULTS

The study found no statistically significant relationship between age and the number of vertebrae involved in the ankylosis (r=0.215; p=0.161) when the whole sample was considered, or when individuals were analysed by sex (Females: r=0.536; p=0.059; Males: r=0.216; p=0.242).

The analysis of the 44 individuals with DISH showed a remarkably consistent pattern of ankylosis. The lower thoracic vertebrae, specifically T10 (41/44, 93.2%), T9 (41/44, 93.2%), T8 (38/44; 86.4%) followed by T7 (35/44; 79.5%) and T11 (29/44; 65.9%) are the most commonly affected vertebrae in DISH patients (see Supplementary Data 1). The analysis also showed that at either end of the main block of ankylosed vertebrae, there are usually a variable number of vertebrae with touching outgrowths. Beyond these vertebrae with touching outgrowths, some vertebral bodies show isolated non-touching bone outgrowths (Figure 1). As already observed by Forestier and Rotés-Querol (1950), the structure of all types of outgrowths (when it was possible to observe the internal structure, for example in outgrowths with post-mortem breaks) mirror that of the normal bone, with a well-organized and smooth cortical bone externally and trabecular bone internally, as if this ossification were an extension of the vertebral body itself. Furthermore, unlike vertebral osteophytes, DISH-related outgrowths in all stages of development are usually rooted at the central third or at the interphase between the central and the upper or lower sections of the sides of the vertebral body, and are vertically oriented and curve around the intervertebral disk.

In all cases, the ossification was located at the antero-lateral surface of the vertebral bodies, but the ossification shifts its position as follows: on the first four thoracic vertebrae the ossification is located on the central third of the vertebral body; from the 5th to the 10th thoracic vertebrae, the ossification shifts to the right half of the vertebrae. Finally, from T10 to L5, the ossification usually splits in two and shifts to the lateral thirds of the vertebral body (Figure 2). However, in cases of very advanced DISH, the left side of the thoracic segment as well as the central third section of the lower thoracic and the lumbar segments can also show ossifications. These are typically smaller and less voluminous and do not tend to form a continuous sheath of more than two vertebrae, as it is commonly seen in the right side.

In the clinical literature, there has been some discussion regarding the co-existence of discarthrosis and DISH. As both conditions are age-related, their co-existence is possible (see Figures 3A and 3B). As the prior presence of soft tissue bridging in DISH would theoretically prevent the degeneration of the intervertebral disk, an inverse relationship between discarthrosis and DISH was expected. As it is clear from Figure 4, the majority of the vertebrae showing a combination of DISH and degeneration of the endplate or DISH and discarthrosis are located in the lumbar section of the spine beyond the reach of the main completed ankylosis. These results suggest that both conditions can co-exist in the same spine, but that the areas with more advanced DISH seem to show a lower probability of being affected by discarthrosis. This co-morbidity seems to be much more common in the lumbar vertebrae (see Supplementary Data 1).

With regards to the relationship between the size of ESM and the extension of the vertebral ankylosis and age, it was hypothesized that if the presence of the spinal ankylosis and the extra-spinal entheseal changes were part of the same condition, then a correlation between the extent of the spinal lesions and the size of the entheseal changes might exist, but no statistically significant correlation was observed between the total number of ankylosed vertebrae and the size of the enthesopathy at the ulnae (right: $r= 0.074$, $p=0.646$; left: $r= 0.232$, $p=0.139$), patellae (right: $r= 0.029$, $p=0.864$; left: $r= 0.176$, $p=0.289$) or calcanei (right: $r= 0.295$, $p=0.068$; left: $r= 0.224$, $p=0.160$). Tables 4A, 4B and 4C show the classification of the individuals according to the size of the enthesopathic changes observed at the insertion of the tendons of *M. triceps brachii* (ulnar olecranon process), *Mm. quadriceps femoris* (proximal surface of patella and tibial tuberosity), *M. gastrocnemius* and *M. soleus* (calcaneal tuberosity). These tables only show individuals whose right and left elements were present. Following Kacki and Villotte's (2005) rationale of imposing a 2mm threshold to attempt to separate the peripheral enthesophytes associated with DISH and that resulting from microtrauma and age, Table 4D summarizes the percentage of individuals showing enthesophytes smaller or larger than 2mm. These results demonstrate a high inter-individual variability in the presence and size of the extra-spinal manifestations as some individuals show well developed enthesophytes in all the locations; some individuals with no or very enthesophytes in any of the locations, and some individuals possess enthesophytes in some, but not all, of the locations (see Supplementary Data 2). This study found no correlation between the size of enthesophytes and the age at death of the individuals (right ulna: r= -0.270, p=0.088; left ulna: r= -0.291, p=0.061; right patella: r= -0.405, p=0.013; left patella: r= -0.320, p=0.042; right calcaneus: r= -0.374, p=0.019; left calcaneus: r= -0.272, p=0.085).

DISCUSSION

It is worth noting that neither the population sample from the WM Bass Donated Skeletal Collection, nor the subsample of individuals with DISH are demographically representative of the US population; thus, this paper will not attempt to extrapolate the demographic findings to the wider population. The absence of correlation between age-at-death and the number of vertebrae involved in the ankylosis was unexpected but possibly related to inter-individual variability (see Supplementary Data 1) and to the limited sample size (n=44).

Confirming the hypothesis that earlier stages of the condition should be observable at either side of the main block of ankylosed vertebrae, this research showed that beyond the main body of ankylosis, there are usually a variable number of vertebrae with touching outgrowths and, beyond these, some vertebral bodies show isolated non-touching bone outgrowths (Figure 1 and Supplementary Data 1). These observations concur with the descriptions by Crubézy (1989) and Fornasier et al. (1983). Crubézy (1989: 110) noted that “sometimes, in isolated vertebrae or in two non-contiguous vertebrae, thin flowing ossifications rooted off to the sides of the spinal plateaus can be seen” and suggested these lesions to be classified as “probable early hyperostosis”. A retrospective anatomical morphological and radiographic study of the changes observable at the insertion of the spinal longitudinal ligaments carried out by Fornasier et al. (1983) defined three stages of development in the lesions associated with DISH: 1) flattened spurs arise from the periphery of the waist of the vertebral body at the entheseal insertion, 2) progression of the spurs become linear bone depositions running adjacent to the vertebral body and 3) new bone from adjacent vertebrae join to form a solid bone bridge. The authors noted that interruptions in the ossification at the level of the intervertebral disk space were common (Fornasier et al. 1983). The non-preservation of the intervertebral disk in human remains does not make it possible to evaluate the distance between the DISH-outgrowths, nor how much of the disk height had been occupied by the outgrowth. However, the location, characteristics and progression of the lesions observed in dry bone in this study correspond with the description of the lesions observed in the CT scans and reported by Kuperus et al. (2019) and by Yaniv et al. (2014).

These isolated outgrowths show the same internal and external structure as the DISH-associated ankylosis, i.e. a well-organized and smooth cortical bone externally and trabecular bone internally, are commonly at the central third or at the interphase between the central and the upper or lower sections of the sides of the vertebral body, and are vertically oriented and curve around the intervertebral disk. These characteristics concur with the original description of the internal and external structure of the DISH-related lesions offered by Forestier and Rotés-Querol (1950): “these hyperostoses have a bony structure with a dense cortex similar to that of the head of the femur, the cancellous bone being in continuity with that of the vertebral bodies” (Forestier and Rotés-Querol 1950: 328). Maat et al. (1995) also noted, that unlike DISH, vertebral osteophytes typical of discarthrosis are not infilled with well-organized trabecular bone, usually have a rough surface and are characterized by a horizontal orientation (Maat et al. 1995). This set of features makes it possible to suggest that the isolated outgrowths found at either end of the DISH-associated ankylosed segment represent its earliest stages of development and makes it possible to differentiate the early stages of DISH from osteophytes. This therefore suggests that early development of DISH lesions can be identified not only in the clinical setting but also in skeletonized human remains.

The pattern of affected vertebrae observed in the individuals from the Bass Collection analysed here concur with the previously published reports indicating that the lower thoracic vertebrae are most commonly affected (Harris et al. 1974; Kuperus et al. 2018). The shifting distribution of ankylosis – central third of the vertebral body between T1-4; right half of the vertebra between T5-10 and to the lateral third of the vertebral body between T10-L5 confirms that the formation of the voluminous ossification avoids the location and/or pulsation of the descending aorta (Forestier and Rotes-Querol 1950; Kuperus et al. 2018). In cases of very advanced DISH, the left side of the thoracic segment and the central third section of the lower thoracic and the lumbar segments can also show ossifications that are typically smaller and less voluminous compared to the right ones and do not tend to form a continuous sheath of more than two vertebrae (Harris et al. 1974; Resnick et al. 1978).

The distribution of ankylosing outgrowths suggests that, contrary to what has been consistently indicated (e.g. Resnick et al. 1975; Kiss et al. 2002), DISH outgrowths are not the result of the ossification *of* the anterior longitudinal ligament. This was first noted by Forestier and Rotés-Querol (1950:326): "the intervertebral ligament is clearly visible and slightly pushed to the left by the ossification" further indicating that the "ligament may easily be detached from the [outgrowths] though it is firmly attached at the level of the vertebral bodies as well as at the level of the disks." Anatomically, the anterior (vertebral) longitudinal ligament is the connective tissue connecting the basio-occipital region to the anterior surface of the sacral promontory. While little research has been carried out on the anatomy of this ligament, it is located at the *central third of the anterior surface* of the spine and seems to be formed by fibers of various lengths: the deep short intervertebral fibers, the intermediate fibers spanning two or three vertebrae and the most superficial ones spanning three or four vertebrae. The anatomical location of the ligament thus does not fully correspond with the lateralized distribution of the main ossification of DISH nor with the possibility of developing contralateral lesions because these usually envelop half of the entire intervertebral space. This suggests that DISH outgrowths are not the result of the ossification *of* only the anterior longitudinal ligament, but rather of the connective tissue in the same region. This would include part of the anterior longitudinal ligament, of the paravertebral connective tissue (such as the continuous perivertebral fibrous sheath formed by short fibers inserting into adjacent vertebrae and extending anterior to the disk), and even sometimes the peripheral part of the disk (Forestier and Rotes-Querol 1950: 329; Forestier and Lagier 1971: 69).

This study has demonstrated that the relationship between discarthrosis and DISH is not straightforward. Both conditions affect the older part of the population, so hypothetically there is the possibility of both co-existing in the same individual. Interestingly, some diagnostic criteria allow for the co-existence of the two features (Utsinger 1985; Crubézy and Crubézy-Ibanez 1993) while others refrain from a positive diagnosis of DISH in the presence of discarthrosis (Resnick and Niwayama 1976; Arlet and Mazières 1985; Rogers and Waldron 1995; Kacki and Villotte 2006). This study shows that both conditions can co-exist in the same spine, but they seem to share an inverse relationship: the more advanced the development of DISH, the lower the probability that the same vertebrae will show signs of spinal osteophytes (Figures 3A and 3B). The fact that this co-morbidity is much more common in the lumbar vertebrae is possibly associated with the higher prevalence of discarthrosis in this lower vertebral region area than in the cervical or thoracic sections (see Supplementary Data 1). In view of these results, it is possible to suggest that the development of a vertebral bridge acts as a protection against the age-related degeneration of the endplate, and thus the lower thoracic vertebral disks are most frequently protected.

The high inter- and intra-individual variability in the presence and size of extra-spinal manifestations repeatedly associated with DISH seen in this study add to the discussion around the relationship between the spinal and the extra-spinal manifestations of DISH (Mader et al. 2012, Kuperus et al. 2017) and to question the idea that these two features are part of the same pathogenic process. It is possible that these results are a reflection of the level of inter-individual variability in the presentation of DISH, but the possibility that the presence of the ESM is not (or not only) related to the presence of spinal lesions, and thus to DISH, but rather is part of an erratic and variable aging process should be contemplated (Shaibani et al. 1993; Stirland 1998; Wilczak 1998; Cardoso and Henderson 2010). Specifically, with regard to the study archaeological human remains, this high inter-individual variability renders the ESM not fit to be used as a proxy for DISH when the spine cannot be analyzed.

Individuals with DISH have been described previously as “bone formers” (Rogers et al. 1997) or as suffering from an ossifying diathesis (Resnick et al. 1978). The lack of consensus in the clinical sphere around the association between the spinal and the extra-spinal manifestations of DISH might suggest that the association between bone formation at entheses and DISH is not simple and direct. This study found significant inter-individual variability in the presentation of the peripheral enthesophytes, suggesting that the predisposition to excessive bone formation might not be part of the pathogenesis of DISH, *if* DISH is primarily defined by the presence of ankylosis at the anterolateral surface of the vertebral column. It is possible that further investigation of the physiology and pathogenesis of DISH might result in its re-classification as an ossifying diathesis affecting multiple locations, including the location of the spinal DISH outgrowths and ESMs, but this is beyond the scope of this study.

Conclusions

The results of this study show that isolated bone outgrowths located at either side of the well-developed and ankylosed outgrowths probably represent the earliest stages of the condition and are usually unaccompanied or accompanied by only mild endplate degeneration. The lesions pathognomonic of DISH appear as a spectrum (isolated, interlocking or touching and ankylosed), but while the diagnosis of DISH still depends on vertebral ankyloses, its early (or pre-DISH) lesions can be identified. These results also pose questions for the idea that the extra-spinal manifestations traditionally associated with DISH are related to the main spinal lesion, but a larger sample size that includes individuals of the same age range, but without DISH, are needed to evaluate the presence of enthesophytes in individuals without DISH and the relationship between spinal lesions and ESM.

The next steps in the investigation of DISH should evaluate the size and distribution of extra-spinal enthesophytes on a large identified collection – regardless of DISH status – to obtain a clearer understanding of the relationship between these two manifestations, their relationship to sex, and the influence of age in their development. Nonetheless, our results concerning extra-spinal enthesophytes caution against diagnosing DISH in the absence of the thoracic portion of the spine.

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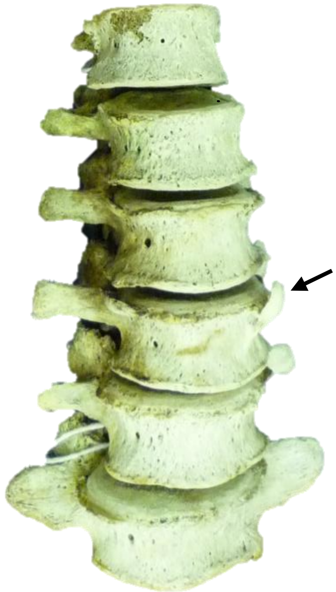
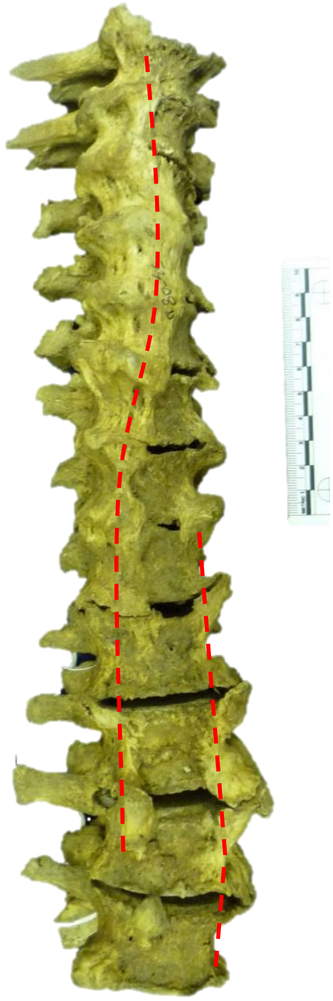
FIGURES

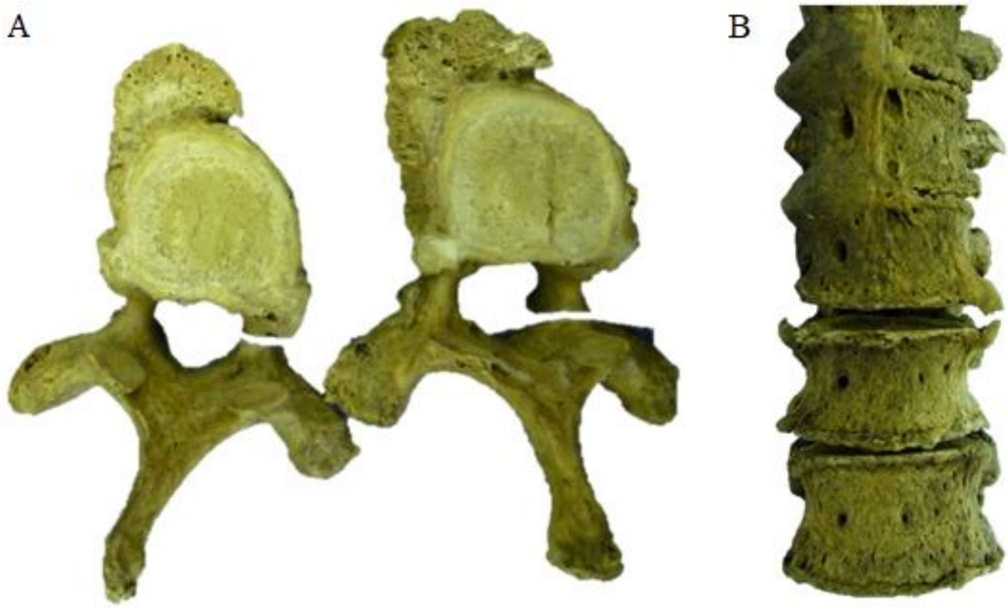
1. Image of an isolated outgrowth at the left half of the 3rd lumbar vertebra as indicated by the arrow. Individual 7, male, 57 years old at the time of death



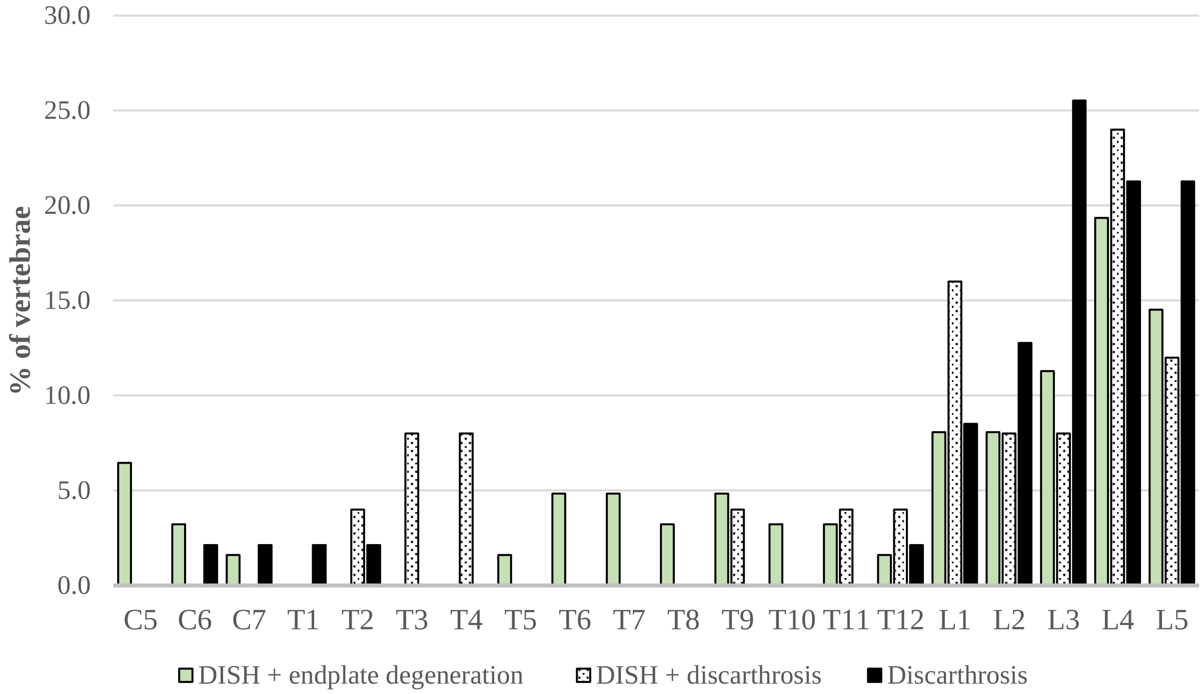
2. Shift in the position of the ossification. Individual 14, male, 65 years of age at the time of death



3. Relationship between DISH, endplate degeneration and discathrosis. A) Well-developed touching outgrowth in thoracic vertebrae with no trace of disk degeneration. B) Combination of discarthrosis and DISH outgrowths in the thoracic and lumbar vertebrae.



4. Location of the DISH lesions with endplate degeneration, with discarthrosis and vertebrae showing only discarthrosis. No lesions were observed in C1 to C4, so there are omitted from the graph.



TABLES

Table 1: Types and characteristics of the outgrowths found in the spine

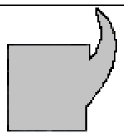
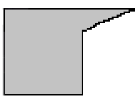
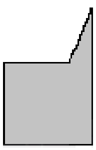
Outgrowth type	**Origin**	**Shape/orientation**	**Assoc. condition**	**References**
	Central third portion of the vertebral body	Candle-like or flowing ossification	DISH	Forestier and Rotes-Querol (1950); Crubézy (1989)
 osteophyte	Superior or inferior endplate margin	Horizontal. When developed, can adopt a vertical orientation	Vertebral osteophytes - discarthrosis	Steinbock (1976); François et al. (1995); Maat et al. (1995)
 syndesmophyte	Superior or inferior endplate margin	Vertical orientation	Ankylosing spondylitis	Chanchairujira et al. (2004)

Table 2: Summary of the characteristics of the different diagnostic criteria for DISH in clinical medicine and in osteoarchaeology

		Resnick & Niwayama (1976)	Arlet & Maziéres (1985)	Utsinger (1985)	Crubézy (1989)	Crubézy & Crubézy-Ibanez (1993)	Rogers & Waldron (1995)	Ortner (2003)	Kacki & Villotte (2006)
	Criteria based on	X-ray findings	X-ray findings	X-ray findings	Utsinger (1985)	Human remains	n/a	Smythe & Littlejohn (1998)	Utsinger (1985)
Spinal	Antero-lateral flowing ossification	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Ankylosis discontinuity[a]	Yes	n/a	Yes	n/a	n/a	Yes	n/a	Yes
	Unilateral	Yes	n/a	n/a	Right	Yes	Right	n/a	n/a
	Definitive DISH[b]	≥4 in thoracic	≥3 in low thoracic	≥4 in thoraco-lumbar	3 in low thoracic	3 in low thoracic	≥4	4	≥4
	Prob./poss. DISH[c]	3 in thoracic	2 in low thoracic	2 (thoracic)	2 in thoracic	2	<4	n/a	≥2
	Cervical involvement	n/a	Yes[d]	n/a	Yes[d]	n/a	n/a	n/a	n/a
	Lumbar involvement	n/a	Yes[d]	n/a	Yes[d]	n/a	n/a	n/a	n/a
	Apophyseal joint	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved
	Intervert. disk space	Retained	Retained	Retained	Retained	Retained	Retained	Retained	Retained
	Discarthrosis	No	No	Yes[d]	n/a	n/a	No	n/a	n/a
	Sacroiliac joint	Unaffected	Unaffected	n/a	AS bridging	AS bridging	AS bridging	Unafected	Unaffected
Extra-spinal	Enthesophytosis	n/a	n/a	AS bridging	Yes (>3mm)	Yes	Yes	n/a	Yes (>2mm)
	Presence	n/a	n/a	Yes (>3mm)	Symmetrical	Yes	Yes	n/a	Yes
	Patella tufting	n/a	n/a	Symmetrical	Yes	Yes	Yes	n/a	Yes
	Heel spurs	n/a	n/a	Yes	Yes	Yes	Yes	n/a	Yes
	Olecranon tufting	n/a	n/a	Yes	Yes	Yes	Yes	n/a	Yes
	Tibial tub. Spurs	n/a	n/a	Yes	n/a	No	Yes	n/a	n/a
	Lig. flavum ossif.	n/a	n/a	n/a	n/a	n/a	Yes	n/a	n/a
	Sacroiliac lig. ossif.	n/a	Yes[d]	n/a	n/a	n/a	n/a	n/a	n/a
	Iliolumbar lig. ossif.	n/a	Yes[d]	n/a	n/a	n/a	n/a	n/a	n/a

The shaded features are the ones which are shared amongst all the authors. n/a: non-applicable: the diagnostic criteria do not include this parameter. [a]: the definition accepts that some bone bridges might not be completely fused. [b]: number of vertebrae required to issue a definitive diagnosis of DISH. [c]: number of vertebrae required to issue a probable or possible diagnosis of DISH [d]: the criteria required in order to diagnose the occurrence of the feature.

Table 3: Biological information of the individuals analysed

ID	Sex	Age (years)	ID	Sex	Age (years)
1	M	51	**26**	M	73
2	M	52	**27**	M	75
3	M	54	**30**	M	78
4	M	55	**31**	M	79
5	M	56	**32**	M	81
6	M	56	**33**	M	81
7	M	57	**34**	M	81
8	M	61	**36**	M	88
9	M	61	**37**	M	89
10	M	61	**38**	F	55
11	M	63	**39**	F	61
12	M	63	**40**	F	63
13	M	64	**42**	F	67
14	M	65	**43**	F	68
15	M	66	**44**	F	69
17	M	67	**45**	F	75
18	M	68	**46**	F	75
20	M	69	**47**	F	77
21	M	71	**48**	F	80
22	M	71	**50**	F	82
23	M	71	**51**	F	84
24	M	72	**52**	F	89

Sex: F: female; M: male. Following the Data Protection Guidelines from the WM Bass Donated Skeletal collections, identification numbers (ID) have been given to all individuals from this sample.

Table 4: Characterization of the enthesophytes at the insertions of *M. triceps brachii (A), Mm. quadriceps femoris (B)* and Achilles tendon (C). D summaries the percentage of individuals showing ESM smaller and bigger than 2mm at these same insertions.

A.

		Left ulna					
		smooth	uneven	1 - 1.99mm	2 - 9.9mm	>10mm	Total
Right ulna	smooth	15	0	0	2	0	17
	uneven	0	3	1	0	0	4
	1 - 1.99mm	3	2	8	6	0	19
	2 - 9.9mm	0	0	0	1	0	1
	>10mm	0	0	0	0	0	0
	Total	18	5	9	10	0	41

B.

		Left patella					
		smooth	uneven	1 - 1.99mm	2 - 9.9mm	>10mm	Total
Right patella	smooth	3	1	1	0	0	5
	uneven	0	2	0	0	0	2
	1 - 1.99mm	0	0	2	0	0	2
	2 - 9.9mm	0	1	0	10	2	13
	>10mm	0	0	0	4	8	12
	Total	3	4	3	14	10	34

C.

		Left calcaneus					
		smooth	uneven	1 - 1.99mm	2 - 9.9mm	>10mm	Total
Right calcaneus	smooth	3	1	1	0	0	5
	uneven	0	2	0	0	0	2
	1 - 1.99mm	0	0	2	0	0	2
	2 - 9.9mm	0	1	0	10	2	13
	>10mm	0	0	0	4	8	12
	Total	3	4	3	14	10	34

D.

	Right and left <2mm	**Right and/or left >2mm**
Ulnae	78% (32/41)	22% (9/41)
Patellae	26.5% (9/34)	73.5% (25/34)
Calcanei	18% (7/39)	82% (32/39)